ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 13 November 2019

Addressee: [redacted]

Decision number: CCH-D-2114489564-34-01/F
Substance name: 2,5-bis-isocyanatomethyl-bicyclo[2.2.1]heptane
EC number: 411-280-2
CAS number: 74091-64-8
Registration number: [redacted]
Submission number: [redacted]
Submission date: 26/06/2018
Registered tonnage band: [redacted]

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**
2. **Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce some toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.**

You have to submit the requested information in an updated registration dossier by ***20 May 2022.*** You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by Wim De Coen, Head of Unit, Hazard Assessment

[1] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

TOXICOLOGICAL INFORMATION

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

Your registration dossier contains for multiple endpoints adaptation arguments according to Annexes XI Sections: 1.2., 1.5, 3, and Annex IX 8.7 column 2 of the REACH Regulation. ECHA has assessed first the scientific and regulatory validity of your general adaptations according to Annex XI Sections 1.5 and 3; Annex IX, before the individual endpoint-specific adaptations according to Annex XI Section 1.2 (Sections 2 and 3).

Evaluation of general and further adaptations

You have sought to adapt information requirements by applying adaptation approaches in accordance with Annexes XI, Sections 1.5 and 3, and Annex IX Section 8.7 Column 2, for the endpoints:

- Toxicity to reproduction;
- Developmental toxicity/teratogenicity.

I. Adaptation: grouping and read-across approach

According to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances[2]. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus,

[2] Please see for further information ECHA *Guidance on information requirements and chemical safety assessment* (version 1, May 2008), Chapter R.6: QSARs and grouping of chemicals.

physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis[3]- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

You consider to achieve compliance with the REACH information requirements for the registered substance "reaction mass of 2,5-bis(isocyanatomethyl)-bicyclo[2.2.1]heptane and 2,6-bis(isocyanatomethyl)-bicyclo[2.2.1]heptane" ([redacted] EC number: 411-280-2, CAS number: 74091-64-8) using data of structurally similar substances "1,3-bis(isocyanato-methyl)-benzene" ([redacted] EC No 222-852-4, CAS No 3634-83-1) (hereafter the 'source substance').

You have provided a read-across documentation as a separate attachment.

You use the following arguments to support the prediction of properties of the registered substance from data for reference substance(s) within the group by interpolation to other substances in the group: "*based on the fact that the presence of two [*isocyanate] *functional groups in the molecular structure of a chemical, without the presence of another functional group.*" As an integral part of this prediction, you propose that the source and registered substance(s) have similar properties for the above-mentioned information requirements. ECHA considers that this information is your read-across hypothesis. ECHA considers that this information is your read-across hypothesis.

ECHA's evaluation of the grouping and read-across approach

Your proposed adaptation argument is that the similarity in chemical structure and in some of the physico-chemical and toxicological properties between the source and registered substance is a sufficient basis for predicting the properties of the registered substance for other endpoints.

Structural similarity is a prerequisite for applying the grouping and read-across approach. However similarity in chemical structure and similarity of some of the physico-chemical and toxicological properties does not necessarily lead to predictable or similar human health properties in other endpoints. Your justification based on structural similarity, similar physico-chemical and toxicological properties has not established why the prediction is reliable for the human health end-points for which the read across is claimed. In particular, ECHA notes that there is evidence from the available *in vitro* and *in vivo* studies that the target and the source substance have also dissimilarities in their physico-chemical and toxicological profiles, or that the available data does not allow a decisive conclusion (e.g. log Pow). More specifically, the

[3] Please see ECHA's Read-Across Assessment Framework (https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across).

available data on oral acute and oral sub-acute toxicity studies demonstrates differences in concentrations causing toxic effects by a factor of two to seven. While this could be incidental and based on differences in the dosing regime for the repeated dose toxicity study, the effects seen with the registered substance are more severe and concern organs related to reproduction and the endocrine system. Furthermore, there are differences reported for *in vitro* chromosomal aberration.

Additionally, ECHA has taken into account all of your arguments together. ECHA firstly notes that you have not provided a reasoning as to why these arguments add to one another to provide sufficient basis for read-across. Secondly, the defects of each individual argument are not mitigated by the other arguments you have provided, and so ECHA considers that the arguments when taken all together do not provide a reliable basis for predicting the properties of the registered substance.

Conclusion on the grouping and read-across approach

Therefore, ECHA considers that this grouping and read-across approach does not provide a reliable basis whereby the human health effects of the registered substance may be predicted from data for reference substance(s) within the group. Hence, this approach does not comply with the general rules of adaptation as set out in Annex XI, Section 1.5. of the REACH Regulation.

As described above, further elements are needed to establish a reliable prediction for a toxicological or ecotoxicological property, based on recognition of the structural similarities and differences between the source and registered substances. This could be achieved (if it is possible) by a well-founded hypothesis of (bio)transformation to a common compound(s), or that the registered and source substance(s) have the same type of effect(s), together with sufficient supporting information to allow a prediction of human health properties.

Further Adaptations

Also, you have sought to adapt the information requirement according to Annex XI Sections 1.2. and 3; and Annex IX Section 8.7 Column 2; and provided the following justification:

"The registered substance is a skin corrosive, seriously eye damaging, a skin and respiratory sensitizer (cat 1A, and cat 1, respectively). It is severely toxic upon inhalation. In addition, the sub-chronic inhalation toxicity study in rats did not show systemic effects but severe local effects were observed causing severe damage to the respiratory tract resulting in STOT RE Cat.1 classification (Route of exposure: inhalation; affected organs: respiratory tract). These effects appear at a dose at least a factor 20 lower compared to systemic effects (NOAEC is 0.12 mg/m3 and ≥2.03 mg/m3 for local and systemic effects respectively).
Moreover, the substance is not mutagenic and therefore, this also does not give any indication for possible systemic effects, including effects on the reproduction/development. The substance showed testes atrophy at 2000 mg/kg in two surviving male rats in an acute oral toxicity study, which was not observed in the 28-d oral study. In addition, a reduction in ovary weights at the highest dose of 500 mg/kg bw/d in a 28-d oral study was observed. However, in the study the ovaries were not examined microscopically. In the acute inhalation and the 90-d inhalation study, there was no effect on ovaries or testes (weight or histopathology) observed. Inhalation is a more relevant route of exposure, since only worker exposure is envisaged, no consumer exposure, thus no effects on gonads are seen, nor expected. [...] *No other related isocyanate substance is known to give such an effect, and in addition, several publications of other isocyanates show that these substances are not reprotoxic or show developmental toxicity (Tyl et al, Toxicol. Sci. 52, p. 248-57 and 258-68, 1999; Gamer et al.,*

Toxicol. Sci. 54, 2000). Moreover, a predictive toxicity assessment of the two constituents of [redacted] *was performed using DEREK (*[redacted] *2014; see report in section 13 of IUCLID). None of the isomers was predicted to give reproduction/developmental toxicity.*
The substance is only used as a monomer for the production of [redacted] *The potential worker exposure is extensively described in chapter 2 of the CSR. This shows that the industrial process is highly controlled, with a limited potential of exposure (only 2 main downstream users, limited activities, and high personal protection measures), with only very low inhalation and dermal exposure possible (see chapter 9 of the CSR). No exposure of consumers, also not via the environment as no emission of the substance takes place (see CSR chapter 9 for an extensive description), is possible. Due to the skin corrosive and sensitizing effects and the local inhalatory effects, stringent personal protective equipment should and will be used as described in the CSR. This personal protection is required to prevent mainly local effects (and sensitization) which occur at much lower effect levels compared to the systemic effects. Based on the toxicological profile, the limited use, with very limited exposure to the substance, and the personal protective equipment used, no hazard and no risk is considered present for reproductive toxicity as well as for developmental toxicity. Therefore, no such study is considered to be required based on REACH Annex XI, section 1 and 3, and column 1 and 2 of Annex IX."*

In support of your proposed adaptation, you have provided the following studies in other sections of the technical dossier:

1) Acute toxicity study in rats by the inhalation route (OECD TG 403, [redacted] 1992)
2) Combined Repeated Dose Toxicity Study with the Reproduction /Developmental Toxicity Screening Test (OECD TG 422, [redacted] 2009) with the analogous substance 1,3-bis(isocyanatomethyl)-benzene [redacted]
3) Sub-chronic toxicity study (OECD TG 413, [redacted] 2000) in rats by the inhalation route with the analogous substance 1,3-bis(isocyanatomethyl)-benzene [redacted]

ECHA has evaluated your adaptation with respect to these adaptations.

II. Adaptation: substance-specific exposure-driven testing

You have sought to adapt the information requirements listed above according to Annex XI Section 3. The provided justification is cited above in Appendix I, Section "*Further Adaptations*", page 4.

ECHA evaluation of substance-specific exposure-driven testing

To fulfil the information requirements the adaptation should meet the general rule for adaptation of Annex XI Section 3.2 where you need to specifically demonstrate that the conditions of sections (a), (b) or (c), as appropriate, are fulfilled. In your dossier you have not clearly specified which particular rule you invoke, but it is understood by ECHA that the adaptation is claimed under Annex XI Section 3.2 (a) or (c). Based on the information in your dossier, adaptation according to Annex XI Section 3.2. (b) seems not to be applicable.

ECHA observes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 3.2.(a), because criteria i), ii) and iii) are not met:

(i) According to the first criterion (i) for 3.2.(a), the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance should demonstrate the absence of or no significant exposure in all scenarios of the manufacture and all identified uses as referred to in Annex VI section 3.5. ECHA observes your argument that ""*The substance is either used* [...] *where very little potential exists for (controlled) exposures, or in a manual process*

line where [...] *During these worker activities, personal protective equipment is being used."* ECHA observes that the use of personal protection equipment in the event of direct exposure does not qualify as "absence or no significant exposure". In addition, you have provided exposure estimates predicted with the tier 1 exposure tool. In order to demonstrate that the requirement of absence or no significant exposure is fulfilled, evidence demonstrating the absence or no significant exposure is required in the dossier for each of the exposure scenarios. You are expected to provide measured data and/or use higher tier exposure modelling tools to strengthen your basis to demonstrate that exposures are absent, or insignificant when compared with the respective DNEL. Therefore ECHA concludes that criterion 3.2.(a)(i) is not met.

(ii) According to footnote (1) of the second criterion (ii) for 3.2.(a), "*a DNEL derived from a screening test for reproductive/developmental toxicity shall not be considered appropriate to omit a prenatal developmental toxicity study or a two-generation reproductive toxicity study*". ECHA notes that you have derived a worker inhalation DNEL for long-term local effects from a repeated dose toxicity study and a worker inhalation DNEL for long-term systemic effects from an acute inhalation study. None of the studies can replace the reproductive/developmental toxicity studies for deriving DNELs. Moreover, as already indicated above, in the technical dossier there is no developmental or reproductive toxicity study that would fulfill this endpoint. Hence, it is not possible to claim that "*no hazard and no risk is considered present for reproductive toxicity as well as for developmental toxicity"*, since the submitted studies do not provide the information required by Annex IX, Section 8.7.2. More specifically, they do not cover key parameters of a pre-natal developmental or extended one-generation reproductive toxicity study, as further explained below in Appendix I Sections 2 and 3. Hence, ECHA concludes that criterion 3.2(a)(ii) is not met.

(iii) Annex XI, Section 3.2.(a)(iii) requires that the results of the exposure assessment show that exposures are always well below the derived PNECs or DNELs. The DNELs for local and systemic long-term inhalation effects were calculated as 0,04 and 0,1 mg/m^3.

For all exposure scenarios (PROCs 1, 3, 8b, 15), the predicted inhalable exposure concentrations reported in the CSR were between [redacted] (taking samples from the mixing vessel) and [redacted] (connecting a drum to the process). The resulting risk characterisation ratios range from [redacted] Hence, based on the information provided in the CSR, all of the estimated exposure concentrations are not considered as being "well below" the derived DNEL. In addition, ECHA observes that the derivation of no-effect levels (DNELs) did not follow the ECHA Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health Version: 2.1 November 2012. Hence, ECHA concludes that criterion 3.2(a)(iii) is not met.

In addition, your adaptation does not meet the requirements of Annex XI 3.2(c), which relates to substances potentially incorporated into an article:

(iv) Regarding Annex XI section 3.2.(c) (i): You indicate in your CSR that "*step 8 - [redacted] - as [redacted] is no longer present at this stage of the process, this is not considered to be a relevant worker activity involving [redacted]*". ECHA observes that you have not provided any evidence for supporting the statement. You have not demonstrated and documented that there is no releases of monomer from the polymer, nor residual monomer in polymer after the polymerisation takes place. Therefore ECHA concludes that criterion 3.2.(c)(i) is not met.

(v) Also the criteria (ii) and (iii) of Annex XI 3.2 (c) are not met because you have predicted exposures as described above and you have not demonstrated and documented that the industrial processes are under strictly controlled conditions. You have described the production process for [redacted] with 11 different steps. Some of the steps, e.g. [redacted] may include manual tasks performed by a worker with personal protective equipment, which cannot be considered as performed under strictly controlled conditions. Hence, ECHA concludes that criteria 3.2. (c)(ii) and (iii) are not met.

Conclusion on substance-specific exposure-driven testing

For the adaptations set in Annex XI, Sections 3.2.(a) and 3.2.(c) to be fulfilled, all conditions (i) to (iii) need to be met for each of those Sections. Hence, since not all criteria are met, Annex XI Sections 3.2.(a) and 3.2.(c) are not fulfilled. Therefore, your adaptation of the information requirement is rejected.

III. Adaptation: Annex IX Section 8.7 Column 2

You have furthermore sought to adapt the information requirements listed above according to Annex IX Section 8.7 Column 2 Third indent. The provided justification is cited above in Appendix I, Section "*Further Adaptations*", page 4.

Evaluation & Conclusion for Adaptation according to Annex IX Section 8.7 Column 2

An adaptation pursuant to Annex IX, Section 8.7 Column 2 Third indent, requires all of three conditions to be fulfilled:(a) the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), (b) it can be proven from toxicokinetic data that no systemic absorption occurs [...] and (c) there is no or no significant human exposure.

ECHA observes that the substance does not meet all of the three conditions, based on the available information. More specifically, the substance is severely toxic for local effects; and systemic effects have been observed in a repeated dose toxicity study by the oral route. Furthermore, for the reasons set out above in Appendix I, "*II. Adaptation: substance-specific exposure-driven testing*", ECHA concludes that it no or no significant exposure has not yet been demonstrated.

Hence, since not all criteria are met, Annex IX Section 8.7 Column 2 is not fulfilled. Therefore, your adaptation of the information requirement is rejected.

Thus, in summary, as stated above, your current registration dossier contains multiple endpoints adaptation arguments according to Annexes XI, Sections: 1.2., 1.5, 3, and Annex IX 8.7 column 2 of the REACH Regulation. ECHA has assessed the scientific and regulatory validity of your general adaptations according to Annex XI Sections 1.5 and, 3; Annex IX, and found all criteria are not met, therefore your adaptations are not fulfilled. Consequently, your adaptations of the information requirements are rejected.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

A "pre-natal developmental toxicity study" (test method OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH

Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The technical dossier does not contain information on a pre-natal developmental toxicity study with the registered substance.

You have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (OECD TG 422, [redacted] 1991) with the analogous substance [redacted] (1,3-bis(isocyanatomethyl)-benzene).

1) Adaptation according to Annex XI Section 1.5 (*grouping and read-across approach*)

You have sought to adapt this information requirement according to Annex XI, Section 1.5. However, as explained in Appendix I section "I Adaptation: grouping and read-across approach" of this decision, above, ECHA notes that your adaptation does not meet the rules for adaptation of REACH Annex XI, Section 1.5. Therefore your adaptation is rejected.

2) Adaptation according to Annex XI Section 1.2 (*weight of evidence*)

You have sought to adapt this information requirement according to Annex XI Section 1.2. The provided justification and supporting information is cited above in Appendix I Section "Further Adaptations", page 4-5.

ECHA's evaluation of the information provided for weight of evidence

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to a pre-natal developmental toxicity study (OECD TG 414). Relevant elements are in particular exposure route, duration and levels, sensitivity and depth of investigations to detect pre-natal developmental toxicity (including growth, survival, external, skeletal and visceral alterations) and maternal toxicity.

ECHA observes that none of the provided studies investigate key parameters of a pre-natal developmental toxicity study like examinations of foetuses for skeletal and visceral alterations. In addition, the provided oral toxicity studies conducted with the registered substance indicate systemic effects including adverse effects on reproductive organs. More specificially, the sub-acute toxicity study exhibits reductions in ovary and adrenal weights in female rats in the absence of body weight changes. The absence of systemic effects in toxicity studies conducted via the inhalation route should not be used to negate these findings, because the local effects by the test material at the site of contact are regarded to be dose-limiting. This is demonstrated by the high-doses being lower in the inhalation studies than in the oral studies.

ECHA's conclusion on weight of evidence

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex IX,

Section 8.7.2. Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

3) Adaptation according to Annex XI Section 3 (*substance-specific exposure-driven testing*)

You have sought to adapt this information requirement according to Annex XI, Section 3(2)a and 3(2)c. However, as explained in Appendix I section "II. Adaptation: substance-specific exposure-driven testing" of this decision, above, ECHA notes that your adaptation does not meet the rules for adaptation of REACH Annex XI, Section 3. Therefore your adaptation is rejected.

4) Adaptation according to Annex IX Section 8.7 Column 2, Third indent

You have sought to adapt this information requirement according to Annex IX, Section 8.7 Column 2. However, as explained in Appendix I section "III. Adaptation: Annex IX Section 8.7 Column 2, Third indent", of this decision, above, ECHA notes that your adaptation does not meet the specific rules for adaptation of REACH Annex IX Section 8.7 Column 2. Therefore, your adaptation is rejected.

Comments on the draft decision

In your comments on the draft decision you state your intention to improve the adaptation according to Annex XI, Section 3. You specify that "*it is the highest priority of the industry to avoid any contact of workers with the substance at any time. As the handling in the supply chain is already optimized to avoid contact, more detailed information on the hazardous properties (resulting from further animal testing) will not provide the information to improve further worker protection.*" In order to strengthen your adaptation, you intend to perform "*workplace monitoring* [...] *to demonstrate absence of exposure in all scenarios of the manufacture and with all identified uses*", and analytical investigations to determine "*Residual monomer in the product and release of the monomer after polymerization from the product...*".

ECHA acknowledges your intention to improve the adaptation. ECHA observes that biomonitoring methods are established for some diisocyanates, and that personal monitoring specific for a substance is more informative of a worker's exposure than static sampling at the workplace. It is your responsibility if you wish to undertake additional studies in order to support an adaptation for the current request. ECHA concludes that all conditions under Annex XI Section 3 (a) or (c) must be fulfilled in order to meet the general rules of this adaptation. ECHA will evaluate the data submitted to fulfil or adapt the information requirement after the deadline of this decision has expired.

Outcome

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

2. Extended one-generation reproductive toxicity study (Annex IX, Section 8.7.3.)

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at [redacted] per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex IX of the REACH Regulation, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD TGs 421 or 422 screening studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity. If the conditions described in column 2 of Annex IX are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

a) The information requirement

ECHA considers that adverse effects on reproductive organs or tissues and/or other concerns in relation with reproductive toxicity are observed. More specifically, the available sub-acute 28d repeated dose toxicity study by the oral route (OECD TG 407, [redacted] 1991) exhibits significantly changed absolute and relative organ weights of ovaries and adrenals. Pursuant to Annex IX, Section 8.7.3. an extended one-generation reproductive toxicity study is thus an information requirement for registrations of the registered substance.

i) The information provided

The technical dossier does not contain information on an extended one-generation reproductive toxicity study with the registered substance.

You did not consider the information requirement for reproductive toxicity in Annex IX, Section 8.7.3., column 1, because no adverse effects on reproductive organs or tissues have been observed in the following available studies:

1) Acute toxicity study in rats by the inhalation route (OECD TG 403, [redacted] 1992)

2) Combined Repeated Dose Toxicity Study with the Reproduction /Developmental Toxicity Screening Test (OECD TG 422, [redacted] 2009) with the analogous substance XDI (1,3-bis(isocyanatomethyl)-benzene)
3) Sub-chronic toxicity study (OECD TG 413, [redacted] 2000) in rats by the inhalation route with the analogous substance XDI (1,3-bis(isocyanatomethyl)-benzene)

More specifically, you explain that "*In the acute inhalation and the 90-d inhalation study, there was no effect on ovaries or testes (weight or histopathology) observed. Inhalation is a more relevant route of exposure, since only worker exposure is envisaged, no consumer exposure, thus no effects on gonads are seen, nor expected.*"

You have provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (OECD TG 422, [redacted] 1991) with the analogous substance [redacted] (1,3-bis(isocyanatomethyl)-benzene).

ii) ECHAs evaluation of the provided information

ECHA points out that the information requirement according to Annex IX, Section 8.7.3. has been changed by Commission Regulation (EU) 2015/282, and that the new information requirement, i.e. the extended one-generation reproductive toxicity study, is an information requirement not only if adverse effects on reproductive organs or tissues have been observed in the available repeated dose toxicity studies (e.g. a 28-day or 90-day repeated dose toxicity study, OECD 421 or 422 screening studies) but also if these studies reveal other concerns in relation with reproductive toxicity. ECHA considers that such concerns in relation with reproductive toxicity are observed from the above studies. ECHA considers the effect on ovaries from an available study with the registered substance via the oral route as potential concern for toxicity to reproduction.

The results from inhalation studies should not be used to negate these findings, due to dose-limiting effects by the irritating and sensitising properties of the registered substance. Hence, an extended one-generation reproductive toxicity study is an information requirement.

1) Adaptation according to Annex XI Section 1.5 (*grouping and read-across approach*)

You have sought to adapt this information requirement according to Annex XI, Section 1.5. However, as explained in Appendix I section "I. Adaptation: grouping and read-across approach" of this decision, above, ECHA notes that your adaptation does not meet the rules for adaptation of REACH Annex XI, Section 1.5. Therefore your adaptation is rejected.

2) Adaptation according to Annex XI Section 1.2 (*weight of evidence*)

You have sought to adapt this information requirement according to Annex XI Section 1.5. The provided justification and supporting information is cited above in Appendix I Section "Further Adaptations", page 4-5.

An adaptation pursuant to Annex XI, Section 1.2. requires sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property with respect to the information requirement in question including an adequate and reliable documentation while the information from each single source alone is regarded insufficient to support this notion.

Your weight of evidence adaptation needs to address the specific dangerous (hazardous) properties of the registered substance with respect to an extended one-generation reproductive toxicity study (OECD TG 443) as requested in this decision. ECHA considers that this study provides, in addition to information to general toxicity, information in particular on two aspects, namely on sexual function and fertility in P0 and F1 generations (further referred to as 'sexual function and fertility') and on development and toxicity of the offspring from birth until adulthood due to pre- and postnatal and adult exposure in the F1 generation (further referred to as 'effects on offspring').

Relevant elements for 'sexual function and fertility' are in particular functional fertility (oestrous cycle, sperm parameters, mating behaviour, conception, pregnancy, parturition, and lactation) in the parental generation after sufficient pre-mating exposure duration and histopathological examinations of reproductive organs in both P and F1 generations. Relevant elements for 'effects on offspring' are in particular peri- and post-natal investigations of the F1 generation up to adulthood including investigations to detect certain endocrine modes of action, sexual development. Also the sensitivity and depth of investigations to detect effects on 'sexual function and fertility' and 'effects on offspring' needs to be considered.

ECHA's evaluation of the information provided for weight of evidence

ECHA observes that none of the provided studies investigate key parameters of an extended one-generation reproductive toxicity study such as 'sexual function and fertility' and 'effects on offspring' at the required level of detailed investigations and statistical power (sensitivity and depth of investigations to detect effects).

In addition, the provided oral toxicity studies conducted with the registered substance indicate systemic effects including adverse effects on reproductive organs. More specificially, the sub-acute toxicity study exhibits reductions in ovary weights in female rats in the absence of body weight changes. The absence of systemic effects in toxicity studies conducted via the inhalation route should not be used to negate these findings, because the local effects by the test material at the site of contact are regarded to be dose-limiting. This is demonstrated by the high-doses being lower in the inhalation studies than in the oral studies.

ECHA's conclusion on weight of evidence

Hence, the sources of information you provided, together with your justification for the adaptation, do not allow to assume/conclude that the substance does not have a particular dangerous (hazardous) property with respect to the information requirement for Annex IX, Section 8.7.3. Therefore, the general rules for adaptation laid down in Annex XI, Section 1.2. of the REACH Regulation are not met and your adaptation of the information requirement is rejected.

3) Adaptation according to Annex XI Section 3 (*substance-specific exposure-driven testing*)

You have sought to adapt this information requirement according to Annex XI, Section 3(2)a and 3(2)c. However, as explained in Appendix I section "II. Adaptation: substance-specific exposure-driven testing" of this decision, above, ECHA notes that your adaptation does not meet the rules for adaptation of REACH Annex XI, Section 3. Therefore your adaptation is rejected.

4) Adaptation according to Annex IX Section 8.7 Column 2, Third indent

You have sought to adapt this information requirement according to Annex IX, Section 8.7 Column 2. However, as explained in Appendix I section "III. Adaptation: Annex IX Section 8.7 Column 2, Third indent", of this decision, above, ECHA notes that your adaptation does not meet the specific rules for adaptation of REACH Annex IX Section 8.7 Column 2. Therefore, your adaptation is rejected.

Comments on the draft decision

In your comments on the draft decision you state your intention to improve the adaptation according to Annex XI, Section 3. ECHA acknowledges your intention, as addressed above in Appedix 1 section 1 of this decision.

iii) *Conclusion on the provided information and adaptations*

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint. Thus, an extended one-generation reproductive toxicity study according to Annex IX, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the required study

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017), the starting point for deciding on the length of the premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required because there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

The highest dose level shall aim to induce some toxicity to allow comparison of effect levels and effects of reproductive toxicity with those of systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results. ECHA notes that there is no study with the registered substance available investigating fertility effects and sexual function. Therefore, you may consider performing a combined OECD TG 422 as such a dose-range finder. This could also serve to verify the effects on ovaries and their relevance to reproductive performance, as indicated by results from the sub-acute repeated dose toxicity study (OECD TG 407, [redacted] 2009), which serve to trigger the extended one-generation toxicity study requested in this decision.

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

Based on the available information, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce some toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation.

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of [Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity)] were identified. However, you may expand the study by including the extension of Cohort 1B, Cohorts 2A and 2B and/or Cohort 3 if relevant information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information shows triggers which are described in column 2 of Section 8.7.3., Annex IX and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* R.7a, chapter R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 07 February 2018.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and did not amend the requests.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix 3: Further information, observations and technical guidance

1. This compliance check decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In carrying out the tests required by the present decision, it is important to ensure that the particular sample of substance tested is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported. If the registration of the substance covers different grades, the sample used for the new tests must be suitable to assess these.

   Furthermore, there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.